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WU-NEAT: A clinically validated, open-source MATLAB toolbox for limited-channel neonatal EEG analysis

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Abstract

Background: Limited-channel EEG research in neonates is hindered by lack of open, accessible analytic tools. To overcome this limitation, we have created the Washington University-Neonatal EEG Analysis Toolbox (WU-NEAT), containing two of the most commonly used tools, provided in an open-source, clinically-validated package running within MATLAB.

Methods: The first algorithm is the amplitude-integrated EEG (aEEG), which is generated by filtering, rectifying and time-compressing the original EEG recording, with subsequent semi-logarithmic display. The second algorithm is the spectral edge frequency (SEF), calculated as the critical frequency below which a user-defined proportion of the EEG spectral power is located. The aEEG algorithm was validated by three experienced reviewers. Reviewers evaluated aEEG recordings of fourteen preterm/term infants, displayed twice in random order, once using a reference algorithm and again using the WU-NEAT aEEG algorithm. Using standard methodology, reviewers assigned a background pattern classification. Inter/intra-rater reliability was assessed. For the SEF, calculations were made using the same fourteen recordings, first with the reference and then with the WU-NEAT algorithm. Results were compared using Pearson's correlation coefficient.

Results: For the aEEG algorithm, intra- and inter-rater reliability was 100% and 98%, respectively. For the SEF, the mean $\pm$ SD Pearson correlation coefficient between algorithms was 0.96 $\pm$ 0.04.

Conclusion: We have demonstrated a clinically-validated toolbox for generating the aEEG as well as calculating the SEF from EEG data. Open-source access will enable widespread use of

common analytic algorithms which are device-independent and unlikely to become outdated as technology changes, thereby facilitating future collaborative research in neonatal EEG.

Keywords

EEG; spectral edge frequency; open source; neonates; quantitative methods; MATLAB

Introduction

Maynard and Prior first developed the analog limited-channel cerebral function monitor (CFM) in the 1960s.¹ The original analog technology was subsequently updated to a digital implementation and validated in neonates by de Vries, Hellström-Westas, Wikstrom and others in the 1980s-90s.²⁻⁶ Current devices are compact, easy to use, and the electrodes have an excellent safety profile for even the most fragile of preterm skin.⁷ The recording can then be analyzed both qualitatively and quantitatively utilizing proprietary software sometimes provided by the manufacturer. As a result, this technology has been used for the study of seizures in preterm infants^{8,9}, maturation changes in EEG background classification over the course of hospitalization^{10,11}, and the early detection of seizures in term infants with hypoxic-ischemic encephalopathy (HIE).¹²⁻¹⁴

Qualitative analysis is performed by visual interpretation of the amplitude-integrated electroencephalogram (EEG), a display derived from the raw EEG signal, allowing the clinician to evaluate cerebral health on a continuum, from normal voltage with sleep-wake cycling, to burst-suppression, to flat tracing. Several standardized methods for interpretation have been developed.^{6,10,15} The digital nature of the recordings also lends itself well to quantitative analysis, ranging from simple measures such as minimum, maximum and mean values, to complex frequency domain techniques evaluating spectral power or calculation of interburst intervals.^{16,17}

Limited-channel EEG monitors with specific application to the neonate were developed by several manufacturers (BrainZ, Olympic, Nicolet) before eventual market consolidation. This has left a field littered with several different proprietary devices, each of which has a unique and incompatible file type. Further compounding this problem is a limited interest in further developing or updating the analysis software by manufacturers (as there is a limited commercial market), necessitating the continued use of software a decade, or more, old. A final challenge is the lack of established specifications for quantitative algorithms, beyond generalities. Heterogeneities in algorithm function may lead to considerable variance in the output, leading to considerable challenges when comparing results collected using devices from different manufacturers.

We have addressed these problems by developing an open source EEG toolbox (WU-NEAT), designed for the analysis of limited-channel EEG recordings of neonates. This set of tools addresses the shortcomings of the current research environment by recreating two key functions of the original aEEG software and providing the framework for development of additional tools. WU-NEAT runs within the widely available MATLAB scientific programming language (The Math Works, Natick MA). As open-source software, the source code for the software is freely available for non-commercial use, reducing barriers to

performing quantitative EEG analysis, allowing inspection of the inner-workings of the algorithms, and standardizing the framework for quantitative EEG, facilitating inter-center comparison.

The key contributions of WU-NEAT are that it:

1. Defines a standardized, open file format for the storage of limited-channel EEG files, enabling long-term interoperability and to prevent it from becoming outdated.
2. Establishes a core framework which enables access to stored files, a modular plugin interface for addition of analytic tools, interactive display of analytic output, and export of results.
3. Implements the two most frequently used tools for analysis of the limited channel EEG in the neonate – amplitude integrate EEG (aEEG) and spectral edge frequency (SEF).

Materials and Methods

EEG recording

EEG recordings used in the development and testing of WU-NEAT were prospectively recorded from preterm infants born before 28 weeks gestation and term infants with hypoxic-ischemic encephalopathy (HIE). A common lead placement technique was used for all infants (C3-P3, C4-P4) and all recordings were made using the BrainZ BRM3 aEEG monitor (Natus Medical, San Carlos, CA). The EEG signals are sampled at 256 Hz, while the impedance is sampled at 1 Hz. The recordings of the preterm infants were 72 hours in length (starting at birth) and the recordings of HIE infants were 96 hours in length (encompassing the entirety of therapeutic hypothermia treatment and rewarming).

The BRM3 generates recordings in the *.BRM binary file format, which cannot be opened by any software package other than the one originally provided by the manufacturer (AnalyZe, Natus Medical, San Carlos, CA). AnalyZe does permit export of the raw two-channel EEG, two-channel impedance recording, and the calculated two-channel aEEG traces as an Excel (Microsoft, Redmond, WA) spreadsheet, although owing to the 32-bit nature of the software, it is limited to export of 65536 rows at a time (approximately 17 minutes of data at 64 Hz). In contrast to the raw EEG signal, exported EEG signals are downsampled to 64 Hz. For the validation component, EEG recordings from 14 infants were fully exported using this method.

File-format specification

As noted, a significant weakness of the current research environment is the lack of a standardized, open file format. Incorporated in this project, we propose a new file format specification which will enable permanent accessibility and guaranteed interoperability between institutions and across computing platforms. For the EEG signals, the comma separated value (CSV) file format will be used to generate a four-column matrix, with the date in column 1 (YYYY-MM-DD), time in column 2 (HH:MM:SS.FFF), the left raw EEG

signal (in μV) in column 3, and the right raw EEG recording (in μV) in column 4. A separate CSV file with four columns will be used to store impedance information with date and time stored in columns 1 and 2, left impedance ($\text{k}\Omega$) in column 3, and right impedance ($\text{k}\Omega$) in column 4. WU-NEAT reads properly formatted CSV files and imports them into MATLAB as datetime or numeric arrays with appropriate labeling.

The open and flexible nature of WU-NEAT allows EEG files from any device to be used. Minimum requirements include a) access to underlying EEG data without encryption or encoding, b) known sampling rate, c) no filtering or modification of the data, d) MATLAB version 2006a or later, and e) the MATLAB Signal Processing Toolbox. The software code and a sample dataset are available for download.¹⁸ Although not used in this validation study, alternate versions of the aEEG algorithm and SEF algorithm are available for the GNU Octave platform, permitting use without the need to purchase additional hardware or software. Significant differences in GUI development tools do not permit the GUI to run within GNU Octave.

Core interface

The tools contained within WU-NEAT can be used as freestanding functions within MATLAB or can be used within a graphical user interface (GUI) which combines data import functions, display of the EEG signal, and selection of data regions for analysis. An example of the interface is shown in Figure 1 and a mind map of the toolbox is shown in Figure 2. The interface is intentionally flexible and modular, allowing for later addition of other analytic tools.

The EEG display functionality contains two components, enabling navigation of the recording and synchronized access of the corresponding raw trace to a selected time point in the aEEG signal. Simultaneous use of raw and aEEG signals is important to improve the specificity of seizure diagnosis and to rule out artifact as the source of a sudden increase in the aEEG baseline¹⁹.

aEEG algorithm

The amplitude-integrated EEG fundamentally is a transformation of the raw EEG signal, one which accentuates EEG activity within the frequency band of greatest interest in the neonate (2-15 Hz) and is time compressed, enabling rapid, longitudinal evaluation of background activity as well as the presence or absence of seizures. The underlying approach to calculation, and interpretation, of the amplitude-integrated EEG has been well described in both analog¹ and digital²⁰ implementations and has been reproduced in WU-NEAT.

To create the aEEG signal, the raw EEG is first passed through an asymmetric pass-band filter (300th-order Parks-McClellan linear-phase FIR filter) which strongly attenuates the signal below 2 Hz (low-frequency physiological artifact) and above 15 Hz (muscle activity, line noise, respiratory and heart rate artifact). The pass-band (2–15 Hz) undergoes gradual amplification with a slope of 12 dB/decade, to compensate for the diminished amplitude of higher frequency EEG activity^{20,21}. The frequency response is shown in Figure 3.

After pass-band filtering, the signal is rectified, and the signal envelope is generated by use of a low-pass Butterworth filter using zero-phase filtering (Figure 4). The resulting transformed signal is displayed in a time-compressed fashion, generally with 3.5 hours of data displayed at a time. In order to accentuate the baseline, a key feature necessary for determination of the aEEG background, the y-axis is a linear-log scale—linear scaling from 0–10 μV and logarithmic from 10–100 μV .

Spectral edge frequency

Power spectral analysis, a method for quantifying the strength of oscillations in a given frequency band has been a commonly used method for signal processing since the development of a digital algorithm by Welch²² in 1967. By quantifying the distribution of spectral power in an EEG recording, Bell et al. were able to delineate¹⁶ the frequency below which 95% of the power resides, a method termed spectral edge frequency (SEF). This approach has been used to confirm the qualitative observation that mean frequency of EEG activity increases with increasing gestational age¹¹ and can identify delayed maturation in infants with brain injury.^{17,23}

A flexible tool for calculating the SEF has been incorporated into WU-NEAT. First, the algorithm partitions the input signal into non-overlapping segments of 60 seconds (3840 samples) in length. In order to eliminate the effects of low-frequency physiologic and high-frequency respiratory, cardiac, and line noise artifact, the selected region of raw EEG signal undergoes pass-band filtering between 2 and 20 Hz using a 100th order FIR filter. The total spectral power of the filtered EEG signal is then calculated using Welch's power spectral density estimate, which divides the signal into 8 segments with 50% overlap. A Hamming window function is applied to reduce spectral leakage. The SEF_x is then calculated at the frequency below which $x\%$ (user defined value) of the spectral power is present.

Validation

All studies procedures were reviewed and approved by the Human Research Protection Office at our institution. All statistical testing was performed in R version 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Sample data

A sample dataset of preterm infants, born before 28 weeks who underwent 72 hours of continuous aEEG monitoring were utilized for validation in the preterm infant. A second dataset of term infants with hypoxic-ischemic encephalopathy who underwent 96 hours of continuous aEEG monitoring were utilized for validation in the term infant. All recordings were derived from previously conducted observational studies.

aEEG validation

As the amplitude-integrated EEG is fundamentally a qualitative tool, validation proceeded qualitatively. For the preterm and term datasets, the aEEG of a 4-hour segment of raw EEG data was calculated first using the algorithm from the manufacturer-supplied software (AnalyZe) and then again using the algorithm in WU-NEAT. The resulting signals were plotted within MATLAB to prevent subtle differences in non-signal plot details from biasing

interpretation. Three authors not involved in the creation of the algorithm (SML, NE, AMM), and who have significant experience in the interpretation of preterm and term aEEGs, were given the resulting plots in random order. They were asked to score the aEEG background using the 5-category (continuous with cyclicity, continuous, discontinuous, burst suppression, flat trace) system developed by Hellstrom-Westas et al.⁶ The percent agreement within raters (to compare output of WU-NEAT and AnalyZe) and between raters (to assess agreement on underlying background pattern) was calculated using Fleiss' Kappa. All statistical work was performed using R v 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

SEF validation

Using the same 4-hour segments of data as in the aEEG validation, the spectral edge frequency was calculated, once using the AnalyZe algorithm and again using the algorithm in WU-NEAT. As the recordings were 4 hours in length, a total of 240 one-minute epochs were compared for each infant. The degree of correlation within each subject was assessed using the Pearson correlation coefficient and averaged across the entire validation cohort.

Results

Sample characteristics

A total of 14 infants were selected for the validation cohort (preterm n=6, term n=8). Mean $\pm$ SD EGA was 25.8 $\pm$ 0.9 weeks for the preterm cohort and 38.2 $\pm$ 2.0 weeks for the term cohort; mean $\pm$ SD birthweight was 845.0 $\pm$ 244.7 grams for the preterm cohort and 2968.0 $\pm$ 637.2 grams for the term cohort (Table 1).

aEEG validation

aEEG traces were successfully produced for all 14 included infants. Examples of the aEEG output from AnalyZe and WU-NEAT are shown in Figure 5. Given that there were three raters and 14 recordings, a total of 42 scores were generated. For the 14 recordings, the predominate background pattern was continuous in 4/14 (28%), discontinuous in 5/14 (36%), and burst suppression in 5/14 (36%). There was complete intra-rater agreement; raters scored all 14 examples with the same background classification when viewing both AnalyZe and WU-NEAT generated images. There was also substantial agreement between raters, with disagreement on the background pattern in only one infant, $\kappa=0.65$. In this case, the aEEG tracing generated by WU-NEAT was scored as discontinuous by two raters and burst suppression by the third rater.

SEF validation

The SEF₉₅ was successfully generated for all 14 infants using the AnalyZe and WU-NEAT algorithms. There was strong correlation between the results, with a mean Pearson correlation coefficient of 0.96 $\pm$ 0.04.

Discussion

Although there is obvious research potential of quantitative, limited-channel EEG in the neonate, the currently available tools for analysis are either non-existent, woefully outdated, or do not directly address the needs of researchers. With WU-NEAT, we have overcome these challenges using an open-source approach, allowing for inspection of the underlying methodology, the ability to add additional tools over time, all in a free, platform-independent package.

Other tools for quantitative EEG analysis are available, but do not sufficiently address the current software gap for limited-channel neonatal EEG. The most prominent example is EEGLAB²⁴, a MATLAB-based software package which contains many quantitative tools. However, EEGLAB was designed for use with conventional (or high-density) EEG recordings of adults. The manner of these recordings is very different from limited-channel EEG in the neonate, and thus many of the built-in functions are inaccessible. Adapting WU-NEAT as an EEGLAB plugin would add additional software dependencies and potential compatibility issues without adding any significant benefit.

A closer match may be found in “Neural,” a package of MATLAB scripts released by O’Toole and colleagues.²⁵ Provided are tools to calculate the spectral edge frequency, the range EEG (similar to aEEG), and the interburst interval. While certainly of interest to many researchers, this toolset lacks a GUI, is missing a method for calculating the aEEG, does not have a standardized file format, and has not been validated against an FDA-approved standard.

The analytic tools provided in WU-NEAT compromise the most commonly used methods for analysis of limited-channel EEG in current clinical practice and research. These tools are encapsulated in an easy to use GUI, which is accessible to investigators of different technical aptitudes. The included components, aEEG and SEF, are the most utilized techniques for limited-channel neonate EEG analysis.

WU-NEAT represents an important first step in re-establishing this neglected field. This extensible framework is now available for the next stage—the creation of novel, innovative tools. The modular and flexible nature of WU-NEAT makes the addition of other algorithms a trivial process, particularly when considering the near-impossibility of such a goal without first developing this foundation.

Limited-channel EEG has been long been plagued questions of inter-rater reliability, in no small part due to differences in hardware and software display. While this issue is less problematic for qualitative scoring systems (such as the Hellström-Westas or Burdjalov systems), it is a critical problem for quantitative analysis. Through the clinical validation provided in this study, users can be confident that the use of WU-NEAT will provide comparable output to the current, FDA-approved commercial standard.

Although aEEG was initially introduced for use in adults, most published investigation recently has been in the neonatal arena. There are no technical reasons why these same tools could not also be used to analyze adult data, however validation of this tool for that purpose

is outside the scope of the authors' expertise. Future lines of investigation should include validation with adult EEG data.

WU-NEAT represents a key step in the establishment of a widely available, standardized platform for quantitative research using limited-channel EEG recordings from neonates. It is our hope that WU-NEAT will be used to develop innovative metrics which can inform or even predict neurocritical events with the aim of ameliorating or even preventing neurologic injury.

Conclusion

An open source implementation of the most common limited-channel EEG analysis techniques (aEEG and SEF) is possible. The resulting algorithms generate numerically equivalent output to the FDA-approved reference standard. Testing with blinded reviewers shows that the output is essentially indistinguishable in clinical use.

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Appendix – Function reference guide

`aeeeg_full.m`

aEEG algorithm

Syntax

```
[aeeeg_output] = aeeeg_full(source_eeg,fs)
```

Description

`aeeeg_full(source_eeg,fs)` returns the calculated amplitude integrated EEG of the input signal *source_eeg*, provided as a single-column numerical vector of raw EEG data. The raw data is first filtered with a 300th order asymmetric Parks-McClellan filter between 2 and 15 Hz. It is rectified and the envelope obtained via low-pass Butterworth filter. The sampling frequency of the raw EEG must be specified as *fs*.

`aeeeg_octave.m`

aEEG algorithm, modified for GNU Octave

Syntax


```
[aeeg_output] = aeeg_full(source_eeg,fs)
```

Description

`aeeg_full(source_eeg,fs)` returns the calculated amplitude integrated EEG of the input signal *source_eeg*, provided as a single-column numerical vector of raw EEG data. The raw data is first filtered with a 300th order asymmetric Parks-McClellan filter between 2 and 15 Hz. It is rectified and the envelope obtained via low-pass Butterworth filter. The sampling frequency of the raw EEG must be specified as *fs*.

The GNU Octave variation has identical syntax to the MATLAB variation but asymmetric filtering is performed using the *remez()* function.

sef.m

Spectral edge frequency algorithm

Syntax

```
[sef_matrix] = sef(source_eeg,sef_level,fs)
```

`sef(source_eeg,sef_level,fs)` returns the spectral edge frequency of the input signal after partitioning into discrete non-overlapping segments. The input signal *source_eeg* should be provided as a single-column numerical vector of raw EEG data. This raw data is first filtered between 2 and 20 Hz using a 100th order FIR passband filter to reduce low-frequency artifact and high frequency muscle and electrical line noise. To calculate SEF, the signal is partitioned into discrete segments (default of 60 seconds) and the total spectral power calculated using *pwelch()*. *sef_level* must be specified as a decimal between 0 and 1, corresponding to the percentage of spectral power below which the threshold is desired. The sampling frequency of the raw EEG must be specified as *fs*.

sef_octave.m

Spectral edge frequency algorithm, modified for GNU Octave

Syntax

```
[sef_matrix] = sef(source_eeg,sef_level,fs)
```

`sef(source_eeg,sef_level,fs)` returns the spectral edge frequency of the input signal after partitioning into discrete non-overlapping segments. The input signal *source_eeg* should be provided as a single-column numerical vector of raw EEG data. This raw data is first filtered between 2 and 20 Hz using a 100th order FIR passband filter to reduce low-frequency artifact and high frequency muscle and electrical line noise. To calculate SEF, the signal is partitioned into discrete segments (default of 60 seconds) and the total spectral power calculated using *pwelch()*. *sef_level* must be specified as a decimal between 0 and 1, corresponding to the percentage of spectral power below which the threshold is desired. The sampling frequency of the raw EEG must be specified as *fs*.

The GNU Octave variation has identical syntax to the MATLAB version. The primary difference is handling data segments containing NaN values. In MATLAB, *pwelch()* reports an error when passed data with missing values. In GNU Octave, an error is not generated but zero is returned as the total spectral power. The GNU variation identifies segments with missing data, skips processing and returns SEF as NaN.

References

1. Maynard D, Prior PF, Scott DF. Device for continuous monitoring of cerebral activity in resuscitated patients. *Br Med J* 1969; 4: 545–546. [PubMed: 5354856]
2. Hellström-Westas L, Rosén I, Svenningsen NW. Silent seizures in sick infants in early life. Diagnosis by continuous cerebral function monitoring. *Acta Paediatr Scand* 1985; 74: 741–748. [PubMed: 4050421]
3. Hellström-Westas L, Rosén I, Svenningsen NW. Cerebral function monitoring during the first week of life in extremely small low birthweight (ESLBW) infants. *Neuropediatrics* 1991; 22: 27–32. [PubMed: 2038424]
4. Wikström S, Pupp IH, Rosén I, et al. Early single-channel aEEG/EEG predicts outcome in very preterm infants. *Acta Paediatr Oslo Nor* 1992 2012; 101: 719–726.
5. Connell J, Oozeer R, de Vries L, et al. Continuous EEG monitoring of neonatal seizures: diagnostic and prognostic considerations. *Arch Dis Child* 1989; 64: 452–458. [PubMed: 2730113]
6. Hellstrom-Westas L, Rosen I, de Vries LS, et al. Amplitude-integrated EEG Classification and Interpretation in Preterm and Term Infants. *NeoReviews* 2006; 7: e76–e87.
7. Davis AS, Gantz MG, Do B, et al. Serial aEEG recordings in a cohort of extremely preterm infants: feasibility and safety. *J Perinatol* 2015; 35: 373–378. [PubMed: 25474559]
8. Shah DK, Zempel J, Barton T, et al. Electrographic seizures in preterm infants during the first week of life are associated with cerebral injury. *Pediatr Res* 2010; 67: 102–106. [PubMed: 19745782]
9. Vesoulis ZA, Inder TE, Woodward LJ, et al. Early electrographic seizures, brain injury, and neurodevelopmental risk in the very preterm infant. *Pediatr Res* 2014; 75: 564–569. [PubMed: 24366515]
10. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. *Pediatrics* 2003; 112: 855–861. [PubMed: 14523177]
11. Vesoulis ZA, Paul RA, Mitchell TJ, et al. Normative amplitude-integrated EEG measures in preterm infants. *J Perinatol Off J Calif Perinat Assoc* 2015; 35: 428–433.
12. Srinivasakumar P, Zempel J, Trivedi S, et al. Treating EEG Seizures in Hypoxic Ischemic Encephalopathy: A Randomized Controlled Trial. *Pediatrics* 2015; 136: e1302–1309. [PubMed: 26482675]
13. Shah DK, Mackay MT, Lavery S, et al. Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. *Pediatrics* 2008; 121: 1146–1154. [PubMed: 18519484]
14. van Rooij LGM, Hellström-Westas L, de Vries LS. Treatment of neonatal seizures. *Semin Fetal Neonatal Med* 2013; 18: 209–215. [PubMed: 23402893]
15. Azzopardi D TOBY study group. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: data from a randomised trial of therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed* 2014; 99: F80–82. [PubMed: 23800393]
16. Bell AH, McClure BG, McCullagh PJ, et al. Spectral edge frequency of the EEG in healthy neonates and variation with behavioural state. *Biol Neonate* 1991; 60: 69–74. [PubMed: 1932388]
17. Inder TE, Buckland L, Williams CE, et al. Lowered electroencephalographic spectral edge frequency predicts the presence of cerebral white matter injury in premature infants. *Pediatrics* 2003; 111: 27–33. [PubMed: 12509550]
18. Vesoulis Z Neonatal EEG Analysis Toolbox (NEAT) Code and Data. Epub ahead of print 6 April 2020 DOI: 10.17632/24N5DK39T4.1.

19. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics* 2007; 120: 770–777. [PubMed: 17908764]
20. Hellström-Westas L, De Vries LS, Rosén I. Atlas of amplitude-integrated EEGs in the newborn. London; Boca Raton, FL: Informa Healthcare ; Distributed in North and South America by Taylor & Francis, 2008.
21. Zhang D, Ding H. Calculation of compact amplitude-integrated EEG tracing and upper and lower margins using raw EEG data. *Health (N Y)* 2013; 05: 885–891.
22. Welch P The use of fast Fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms. *IEEE Trans Audio Electroacoustics* 1967; 15: 70–73.
23. El Ters NM, Vesoulis ZA, Liao SM, et al. Impact of brain injury on functional measures of amplitude-integrated EEG at term equivalent age in premature infants. *J Perinatol Off J Calif Perinat Assoc*. Epub ahead of print 11 May 2017 DOI: 10.1038/jp.2017.62.
24. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004; 134: 9–21. [PubMed: 15102499]
25. Toole JMO. Neural: Quantitative Features For Newborn Eeg In Matlab. Epub ahead of print 16 November 2017 DOI: 10.5281/zenodo.1052810.

Figure 1: Screenshot of the graphical user interface with linked display of the raw trace and associated aEEG and the calculated SEF of the selected region.

Figure 2:
A visualization of the two pathways in which the toolbox can be used (via GUI or individual functions). Sample plots of data at each stage are shown.

Figure 3:
Frequency response of the asymmetric bandpass filter used in the aEEG algorithm, which filters out the signal below 2 Hz and above 15 Hz.

Figure 4:

The output of the enveloping function (the aEEG signal) is shown in black, on top of the filtered, rectified raw EEG signal (gray).

Figure 5:

Example of paired aEEG signals calculated by the AnalyZe reference algorithm (left column) and the WU-NEAT algorithm (right column). Row A is a burst-suppression pattern from a 2-day old 24-week EGA infant. Row B is a continuous pattern with evidence of cyclicity from a 4-day term gestation infant, previously suffering from hypoxic-ischemic encephalopathy, now resolved. Row C is a 2-day old term gestation infant suffering from hypoxic ischemic encephalopathy with a predominant burst-suppression pattern with a 30-minute seizure noted 120 minutes into the recording

Table 1.

Sample Characteristics

	Preterm cohort (n=6)	Term cohort (n=8)
Gestational age, mean (SD), weeks	25.8 (0.9)	38.2 (2.0)
Birth weight, mean (SD), grams	845.0 (244.7)	2968.0 (637.2)
Male sex, n (%)	3 (50)	3 (38)
Apgar score 5 min, median (range)	5 (1-8)	4 (2-5)